UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 5 2005

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Ms. Jessica Sandler, MHS
Ms. Susan L. Hall, Esq.
People for the Ethical Treatment of Animals
501 Front Street
Norfolk, VA 23510

Re: Petition to Compel the U.S. EPA to Promulgate a Rule Relating to Animal Welfare under the Toxic Substances Control Act

Dear Ms. Sandler and Ms. Hall:

Thank you for your petition, dated April 5, 2005, requesting that EPA promulgate a rule to require that all chemical testing conducted in connection with test rules and voluntary consent orders under the Toxic Substances Control Act (TSCA), as well as testing under the voluntary High Production Volume (HPV) Challenge Program, adhere to certain animal welfare principles contained in guidance provided to participants in the voluntary HPV Challenge Program. The Agency has carefully considered your request and is denying the petition for the reasons provided in the enclosed response. EPA's decision to deny the petition in no way reflects a change in the Agency's ongoing commitment and efforts to appropriately consider, encourage, and facilitate animal welfare. Rather, the decision is based on a thorough consideration of how the voluntary HPV Challenge Program animal welfare principles best fit into the structure and implementation of the various TSCA testing authorities and related voluntary programs.

The voluntary HPV Challenge Program animal welfare principles were developed as specific guidance for this Program and may not be appropriate in other contexts. Given this limitation, EPA needs to retain flexibility for future situations not related to this Program. In accordance with TSCA, the Agency is called upon to ensure that adequate data are developed on chemical substances to enable the assessment of risk of injury to health and the environment. The Agency has nonetheless demonstrated its commitment to reducing, refining, or replacing animal testing consistent with that mission, as illustrated in the enclosed response.

Sincerely,

Susan B. Hazen
Principal Deputy Assistant Administrator

Enclosure

RESPONSE TO "PETITION TO COMPEL THE U.S. EPA TO PROMULGATE A RULE RELATING TO ANIMAL WELFARE UNDER THE TOXIC SUBSTANCES CONTROL ACT"

I. Introduction

On April 6, 2005, the U.S. Environmental Protection Agency (EPA) received a petition from the People for the Ethical Treatment of Animals (PETA)[1] requesting that the Agency initiate rulemaking to require that (1) all chemical testing conducted in connection with test rules and voluntary consent orders under the Toxic Substances Control Act (TSCA), as well as testing under the voluntary High Production Volume (HPV) Challenge Program, adhere to certain animal welfare principles contained in guidance provided to participants in the voluntary HPV Challenge Program,[2] and (2) EPA enforce those guidelines where they are not followed. See *Petition to Compel the U.S. EPA to Promulgate a Rule relating to Animal Welfare under the Toxic Substances Control Act* (April 5, 2005), pp. 1-2 and 23. The petitioner asserts that the petition was filed under § 21 of TSCA, 15 U.S.C. § 2620, and the Administrative Procedure Act (APA), 5 U.S.C. §553(e).

For the reasons explained in this response, EPA is denying the petition. EPA's decision in no way reflects any change in the Agency's ongoing commitment and efforts to appropriately consider, encourage, and facilitate animal welfare. Rather, the decision is based on a thorough consideration of how the voluntary HPV Challenge Program animal welfare principles best fit into the structure and implementation of the various TSCA testing authorities and related voluntary programs.

The voluntary HPV Challenge Program animal welfare principles were developed as specific guidance for this Program and may not be appropriate in other contexts. Given this

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[1] The petition (p.1) states that it is also submitted on behalf of "a coalition of national animal, health, and environmental protection organizations" including Physicians Committee for Responsible Medicine, American Anti-Vivisection Society, Alternatives Research and Development Foundation, Doris Day Animal League, Earth Island Institute (Marine Mammal Project), and The Humane Society of the United States.

[2] As discussed in section II.D. below, the voluntary HPV Challenge Program animal welfare principles were distributed in an October 14, 1999, EPA letter to participants in the voluntary HPV Challenge Program. A copy of that letter is attached to this response (Attachment 1). It can also be viewed at www.epa.gov/chemrtk/ceoltr2.htm. Also as described in section II.D., the petition references some related discussion in EPA's December 26, 2000, Federal Register notice at 65 FR 81686. To the extent that the description of these principles in the petition differs from the principles as originally drafted, EPA presumes that the petitioner is requesting rulemaking with respect to the principles as stated in the petition.

limitation, EPA needs to retain flexibility for future situations not related to this Program. In accordance with TSCA, the Agency is called upon to ensure that adequate data is developed on chemical substances to assess their risks of injury to health and the environment. The Agency has nonetheless demonstrated its commitment to reducing, refining, or replacing animal testing consistent with that mission, as illustrated below.

II. Background

A. TSCA Statutory Policy

Congress enacted the Toxic Substances Control Act (TSCA) in 1976 with "the primary purpose of this Act to assure that ... chemical substances and mixtures do not present an unreasonable risk of injury to health or the environment." 15 U.S.C. § 2601(b)(3). Toward that end, Congress declared it the policy of the United States that "adequate data should be developed with respect to the effect of chemical substances and mixtures on health and the environment," 15 U.S.C. § 2601(b)(1), and that "adequate authority should exist to regulate chemical substances and mixtures which present an unreasonable risk of injury to health or the environment. . ." 15 U.S.C. § 2601(b)(2). Section 4(b)(2)(A) of TSCA specifically sanctions "whole animal tests" as a permissible methodology that EPA may prescribe in a standard for development of test data. TSCA contains no provisions related to animal welfare.[3]

B. TSCA Testing Authorities

The petition requests that EPA codify the voluntary HPV Challenge Program animal welfare principles in a mandatory, enforceable rule for "all TSCA testing – be it in the HPV Program, by test rule, or by consent order." Petition p. 23, see also pp. 1-2. Beyond testing conducted via the voluntary programs, EPA can issue mandatory chemical testing requirements via various mechanisms under TSCA § 4 and § 5. These testing authorities include § 4 test rules (15 U.S.C. § 2603, 40 CFR Parts 790 - 799), § 4 Enforceable Consent Agreements (15 U.S.C. § 2603, 40 CFR Parts 790 - 799), and § 5(e) Orders (15 U.S.C. § 2604(e)).

TSCA § 4 provides EPA with authority to promulgate test rules to require health and environmental effects testing of chemical substances or mixtures for which certain statutory findings are made (see TSCA § 4(a)). EPA has broad authority to specify the types of testing required by a test rule, i.e., "The health and environmental effects for which standards . . . may be prescribed include carcinogenesis, mutagenesis, teratogenesis, behavioral disorders, cumulative or synergistic effects, and any other effect which may present an unreasonable risk of injury to health or the environment." TSCA § 4(b)(2)(A).

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[3] TSCA § 4(b)(1) says that "In determining the standards [for development of test data] ..., the Administrator's considerations shall include the relative costs . . . and the reasonably foreseeable availability of the facilities and personnel . . .," but says nothing about animal welfare issues.

EPA also has authority under TSCA § 4 to negotiate enforceable consent agreements (ECAs) and to issue orders incorporating these agreements (see 40 CFR part 790, subparts A, B and D). Such agreements may be used where a consensus exists among EPA and "interested parties," which can include affected manufacturers, processors, and interested members of the public, concerning the need for and scope of testing. Similar to its authority to specify the types of testing required by a TSCA § 4 test rule, EPA may negotiate a broad range of testing for inclusion in an ECA.

Section 5(e) of TSCA authorizes EPA to issue an order to prohibit or limit a new chemical substance or a chemical substance intended for a significant new use. Such orders are typically negotiated as Consent Orders, but EPA has authority under §5(e) to seek mandatory compliance. The heading of §5(e) of TSCA is "Regulation Pending Development of Information" and one of the determinations EPA must make to issue an order under TSCA §5(e) is that "information available to the Administrator is insufficient to permit a reasoned evaluation of the health and environmental effects of a chemical substance..." TSCA § 5(e)(1)(A)(i), 15 U.S.C. § 2604(e)(1)(A)(i).

C. The Voluntary HPV Challenge Program

EPA's voluntary HPV Challenge Program, initiated in 1998 as part of the Agency's Chemical Right-to-Know Initiative (see www.epa.gov/chemrtk), is designed to provide an opportunity to manufacturers of chemicals manufactured or imported into the United States in volumes of 1 million pounds or more per year[4] to make publicly available the baseline level Screening Information Data Set (SIDS) established in 1990 and 1991 by the Organization for Economic Cooperation and Development (OECD).[5] The OECD SIDS is an internationally

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[4] The list of chemicals included in the voluntary HPV Challenge Program were identified based on production volumes reported for the 1990 Inventory Update Rule (IUR, 40 CFR part 710, subpart B). See EPA, OPPT. Chemical Hazard Data Availability Study: What Do We Really Know About the Safety of High Production Volume Chemicals? (April 1998)(www.epa.gov/opptintr/chemtest/hazchem.htm).

[5] For more on the OECD SIDS, see OECD. Decision-Recommendation of the Council on the Cooperative Investigation and Risk Reduction of Existing Chemicals (January 31, 1991), and OECD Secretariat. *Manual for the Investigation of HPV Chemicals*. OECD Programme on the Co-Operative Investigation of High Production Volume Chemicals. Paris, France. December 2003. Available online at http://www.epa.gov/chemrtk/guidocs.htm and http://www.oecd.org/document/7/0,2340,en_2649_34379_1947463_1_1_1_1,00.html/. Additional information on the voluntary HPV Challenge Program is available, e.g., at www.epa.gov/chemrtk/volchall.htm, 65 FR 81686-81698, Dec. 26, 2000, and "Status and Future Directions of the High Production Volume Challenge Program," EPA-743-R-04-001, Nov. 2004 (http://www.epa.gov/chemrtk/hpvstatr.htm). SIDS Manual. Third Ed. Screening Information Data Set Manual of the OECD Programme on the Co-Operative Investigation of High

agreed upon set of basic tests for screening high production volume chemicals for human and environmental hazards. While only about 11 percent of all chemical substances listed on the TSCA Inventory of Chemical Substances are manufactured at 1 million pounds or more annually, these chemicals account for approximately 95 percent by volume of all chemical production in the United States. 65 FR 81662. Studies conducted by Environmental Defense (formerly the Environmental Defense Fund), EPA, and the American Chemistry Council (ACC, formerly the Chemical Manufacturers Association), showed a dearth of publicly available basic toxicity data on many of these chemicals.[6] EPA found that only 7 percent had a full set of publicly available screening data, and 43 percent had no publicly available basic hazard data.[7] The remaining chemicals had only limited data available. A framework for the voluntary HPV Challenge Program was announced jointly on October 9, 1998, by EPA, Environmental Defense, ACC, and the American Petroleum Institute.

EPA has indicated that the voluntary HPV Challenge Program and any TSCA § 4 HPV SIDS test rules "will generally be carried out in a manner consistent with the OECD HPV SIDS Program" to ensure that data developed are mutually comparable and compatible, and to enable international data sharing in order to avoid unnecessary or duplicative testing and its associated costs. 65 FR 81689 and 81692. On December 26, 2000, EPA published Federal Register notices describing the voluntary HPV Challenge Program (65 FR 81686) and proposing the first TSCA § 4 HPV SIDS test rule (65 FR 81658). The December 26, 2000, Federal Register notice on the voluntary HPV Challenge Program identified its three main elements as "1. Fixed timetable and fixed list of chemicals... 2. Continuous public access to program status and results .... 3. International sharing of testing responsibility." 65 FR 81692.

Participation in the voluntary HPV Challenge Program is completely optional, and companies participating in the program do not enter into enforceable commitments.

EPA posts on its website sponsor-generated robust summaries of all data collected in the

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Production Volume Chemicals, Paris, France, July 1997, available at www.epa.gov/chemrtk/sidsappb.htm and www.oecd.org/ehs/sidsman.htm. Additional information on the voluntary HPV Challenge Program is available, e.g., at www.epa.gov/chemrtk/volchall.htm, 65 FR 81686-81698, Dec. 26, 2000, and "Status and Future Directions of the High Production Volume Challenge Program," EPA-743-R-04-001, Nov. 2004.

[6] EPA, OPPT. *Chemical Hazard Data Availability Study: What Do We Really Know About the Safety of High Production Volume Chemicals?* (April 1998) (www.epa.gov/oppintr/chemtest/hazchem.htm); Environmental Defense, *Toxic Ignorance*, New York, New York, (Summer 1997) (www.edf.org/pubs/reports/toxicignorance); American Chemistry Council, *Public Availability of SIDS-Related Testing Data for U.S. High Production Volume Chemicals* (June 12, 1998).

[7] Id. See also 65 FR 81687.

voluntary HPV Challenge Program website.[8] Data collected via the voluntary HPV Challenge Program will allow the Agency, the public, and others to better assess potential risks to health and the environment from these chemicals. As appropriate, this information will be used to ensure a scientifically sound basis for hazard assessment and risk screening, assessment and management actions. The voluntary HPV Challenge Program has generated significant amounts of data, including data generated prior to the inception of the Program, that were not previously publicly available. EPA has found the voluntary HPV Challenge program to be a highly effective and efficient way to obtain needed data.[9]

D. The Voluntary HPV Challenge Program Animal Welfare Principles

1. The October 14, 1999, Letter to Voluntary HPV Challenge Program Participants

The specific set of voluntary HPV Challenge Program animal welfare principles that the petitioner urges EPA to mandate by rule were distributed in an October 14, 1999, guidance letter from Susan H. Wayland, Deputy Assistant Administrator of EPA's Office of Prevention, Pesticides and Toxic Substances (Attachment 1 to this petition response). This letter was sent to all persons who had at that point committed to participate in EPA's voluntary HPV Challenge Program.

In this letter, which petitioner participated in developing, EPA asked HPV Challenge Program participants to observe the following principles as they proceed with the program:[10]

1. In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is sufficient data, given the totality of what is known about a chemical, including human experience, and that certain endpoints need not be tested.

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[8] Comments on test plans are posted on EPA's website at www.epa.gov/opptintr/chemrtk/viewsrch.htm and www.epa.gov/chemrtk/hpvrstp.htm.

[9] For example, as of July 2004, 92% of HPV chemicals had been sponsored. *Status and Future Directions of the High Production Volume Challenge Program*, EPA-743-R-04-001, Nov. 2004, p. 1. See also the related discussion in section III.F. below.

[10] The petition omits without reference an item that was listed as principle number 9 in EPA's October 14, 1999, letter. That principle stated (in part): "Testing of closed system intermediates, which present less risk of exposure, shall be deferred until 2003; (b) Individual chemicals (i.e., those HPV chemicals not proposed for testing in a category) that require further testing on animals shall be deferred until November 2001." EPA presumes that the petitioner does not request that this principle be incorporated into a rule because the dates have already lapsed. EPA's response reflects the same listing of voluntary HPV Challenge Program animal welfare principles as in the petition.

2. Participants shall maximize the use of existing and scientifically adequate data to minimize further testing.

3. Participants shall maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships.

4. Consistent with the Screening Information Data Set (SIDS) program of the Organization for Economic Cooperation and Development (OECD), participants shall not conduct any terrestrial toxicity testing.

5. Participants are encouraged to use in vitro genetic toxicity testing to generate any needed genetic toxicity screening data, unless known chemical properties preclude its use.

6. Consistent with the OECD/SIDS program, participants generally should not develop any new dermal toxicity data.

7. Participants shall not develop sub-chronic or reproductive toxicity data for the HPV chemicals that are solely closed system intermediates, as defined by the OECD/SIDS guidelines.

8. In analyzing the adequacy of screening data for chemicals that are substances Generally Recognized as Safe (GRAS) for a particular use by the Food and Drug Administration (FDA), participants should consider all relevant and available information supporting the FDA's conclusions. Participants reviewing the adequacy of existing data for these chemicals should specifically consider whether the information available makes it unnecessary to proceed with further testing involving animals. As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant.

9. Companies shall allow 120 days between the posting of test plans and the implementation of any testing.

2. Submission of Rationales for Conducting Certain Testing

The petition notes that EPA's December 26, 2000, Federal Register notice on the voluntary HPV Challenge Program (65 FR 81686) "expanded on several items including the following:"

> (a) The Agency stressed the need for justification if any proposed genetic toxicity testing was not to be conducted *in vitro*. If chemical characteristics of the substance precluded *in vitro* testing, the test sponsors were asked "to submit to EPA the rationale for conducting one of these alternative [*in vivo*] tests as part of the test plan." (p. 81695)

> (b) The EPA endorsed the use of the combined repeated-dose/reproductive/developmental toxicity test (OCED 422), which uses approximately 675 animals per test, rather than conducting separate repeated-dose, reproductive tests, and developmental toxicity tests, which kill approximately 40, 1,300 and 1,300 animals, respectively. Again, the EPA cautioned that where the combined reproductive screening study is not proposed, "test sponsors are asked to submit to EPA the rationale for conducting these alternative [separate] tests as part of the test plan" (pp. 81695 and 81697).
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> (c) With respect to acute fish toxicity testing, EPA stated that "for certain HPV chemicals, acute toxicity studies are of limited value in assessing the substances' aquatic toxicity… For the purposes of the HPV Challenge Program… EPA believes that for chemicals determined to have a log K_{ow} equal to or greater than 4.2, the following tests should be conducted: chronic toxicity to daphnia (*in place of* the acute toxicity tests in fish and daphnia…)" (p. 81695, emphasis supplied.) "A sponsor who believes that acute aquatic fish testing is appropriate for an HPV chemical with a high log K_{ow} should provide in its submitted test plan the rationale for conducting such testing."

Petition at page 4.

3. Guidance, Not Requirements

As recognized by the petitioner (Petition pages 1, 4, 23 and elsewhere), the voluntary HPV Challenge Program animal welfare principles were developed as guidance, not as legally binding and enforceable mandates. For the reasons explained in section IV below, EPA believes that the most appropriate way to apply the voluntary HPV Challenge Program animal welfare principles is as guidance, rather than as mandatory requirements.

III. EPA's Demonstrated Commitment to the Voluntary HPV Challenge Program Animal Welfare Principles

The petition principally argues that the voluntary HPV Challenge Program animal welfare principles should be made mandatory because they have been "consistently, repeatedly and deliberately disregarded" by both industry test sponsors and by EPA. Petition at p. 4. EPA disagrees, and this section describes numerous ways in which EPA has acted to communicate and realize implementation of the voluntary HPV Challenge Program animal welfare principles. Discussion of how industry Challenge sponsors have in fact generally acted in accordance with these principles is provided, e.g., in section III.F.

EPA's denial of this petition in no way reflects any change in EPA's ongoing

commitment and efforts to appropriately consider, encourage and facilitate animal welfare. Rather EPA's denial of this petition is based on a thorough consideration of how the voluntary HPV Challenge Program animal welfare principles best fit into the structure and implementation of the various TSCA testing authorities and related voluntary programs. As noted in many previous letters to PETA, EPA has demonstrated its commitment to reducing, refining, or replacing animal testing to the extent testing is necessitated by the important work, as mandated by TSCA, of collecting sufficient information on chemical substances to assess their risks of injury to health and the environment.

Contrary to petitioner's claim that EPA has "consistently, repeatedly and deliberately disregarded" the voluntary HPV Challenge Program animal welfare principles, EPA has been both public and consistent in communicating and realizing implementation of the Agency's commitment to the voluntary HPV Challenge Program animal welfare principles in the context of the voluntary HPV Challenge Program and TSCA § 4 HPV SIDS test rules. EPA has used letters, Federal Register notices and its website to communicate, and in so doing, encourage sponsors to follow the voluntary HPV Challenge Program animal welfare principles. EPA has applied considerable effort to realize implementation of the voluntary HPV Challenge Program animal welfare principles, including developing guidance documents, commenting on individual test plans, and recommending testing alternatives. The following are tangible examples of EPA's substantial efforts to promote the voluntary HPV Challenge Program animal welfare principles:

A. Letters to HPV Participants

First, EPA's Deputy Assistant Administrator for Prevention, Pesticides and Toxics sent the October 14, 1999, letter, dedicated exclusively to promotion of the voluntary HPV Challenge Program animal welfare principles, to all participants in the voluntary HPV Challenge Program. The October 14, 1999, letter states clearly that "I am asking you and your fellow HPV Challenge participants to observe the following principles as we proceed with the program" and "It is the intention of the Agency that the HPV Challenge program, including the test rule(s), should proceed in a manner that is consistent with these principles and concerns."

Secondly, in October 2000, the Agency sent to all HPV Challenge participants and relevant trade associations reminder letters, the sole purpose of which was to "reiterate the Agency's commitment to the principles outlined in the October 14, 1999, letter . . . [and request] that all participants adhere to the principles. . ."[11]

[11] There were two slightly different versions of these letters: one dated October 25, 2000, sent by Susan Wayland to relevant trade associations, and another dated October 31, 2000, sent to all HPV Challenge participants by Charles Auer, then Director of the Chemical Control Division, and Oscar Hernandez, Director of the Risk Assessment Division, Office of Pollution Prevention and Toxics.

B. Federal Register Notices

In the Agency's December 26, 2000 Federal Register notices, EPA discussed in detail the October 14, 1999, letter and how animal welfare issues are being addressed in the voluntary HPV Challenge Program and the proposed TSCA § 4 HPV SIDS test rule, including a solicitation of "comment on the potential approaches that may be used to incorporate the principles contained in the October 14, 1999, letter in the context of TSCA § 4 HPV SIDS rulemakings." See in particular 65 FR 81666, 81691 and 81693. In fact, a significant portion of the discussion in both of these Federal Register notices is devoted to the animal welfare principles, including entire sections on animal welfare and existing data, among other things. Both Federal Register notices state that "EPA is making every effort to ensure that . . . unnecessary or duplicative testing is avoided and the use of animals is minimized." 65 FR 81666 and 81691. Many other relevant points articulated in these Federal Notices are discussed elsewhere in this petition response.

C. Guidance Documents

EPA has generated and posted on its HPV website numerous detailed guidance documents (often lengthy) promoting and facilitating the voluntary HPV Challenge Program animal welfare principles, including use of existing data, categories and structure activity relationship (SAR) analysis, *in vitro* testing, etc. See www.epa.gov/chemrtk/guidocs.htm.

Guidance documents posted on the HPV Challenge website include:

● Fact Sheet on Animal Welfare (EPA 745-F-99-003 (July 2000) at www.epa.gov/chemrtk/anfacs2.pdf;

● Guidance on Searching for Chemical Information and Data at www.epa.gov/chemrtk/srchguid.htm;

● Determining the Adequacy of Existing Data at www.epa.gov/chemrtk/datadfin.htm and www.epa.gov/chemrtk/datadeqfn.pdf;

● Development of Chemical Categories in the HPV Challenge Program at www.epa.gov/chemrtk/categuid.htm and www.epa.gov/chemrtk/catdoc29.pdf;

● The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program at www.epa.gov/chemrtk/sarfinl1.htm and www.epa.gov/chemrtk/sarfinl1.pdf; and

● Guidance for Testing Closed System Intermediates for the HPV Challenge Program at www.epa.gov/chemrtk/closed9.htm and www.epa.gov/chemrtk/closed9.pdf.; and

● Guidance Document on Using *In Vitro* Data to Estimate *In Vivo* Starting Doses

for Acute Toxicity at www.epa.gov/chemrtk/nih2001b.pdf.

D. EPA's Comments on Test Plans

There are numerous examples of Agency comments on test plans submitted for the voluntary HPV Challenge Program that promote and encourage adherence to the voluntary HPV Challenge Program animal welfare principles.[12] The petition (pages 5-20) criticizes approximately 50 of the 333 EPA comments on HPV test plans that the Agency has posted to date, and characterizes EPA's comments as "failing to abide by" the voluntary HPV Challenge Program animal welfare principles. Petition p.5. First, as discussed above, the voluntary HPV Challenge Program animal welfare principles are guidance, which EPA has asked participants to observe. It should also be noted that the test plan comments petitioner criticizes represent only about 15 percent of the total number of cases, a relatively small and selective fraction. More importantly, for the reasons explained throughout this document, the Agency does not agree with most, if not all, of PETA's criticisms.[13]

While the Agency is confident that its actions are consistent with the voluntary HPV Challenge Program animal welfare principles in virtually all cases, the Agency did not attempt in this response to rebut each and every test plan criticism in the petition. In replies to numerous letters from petitioner, EPA has already responded to many of petitioner's criticisms of test plans, some of which petitioner repeats in their petition.[14] Petitioner asserts certain recurring criticisms that are erroneous and evince petitioner's misunderstanding of the voluntary HPV Challenge Program process. For example, the voluntary HPV Challenge Program does not contemplate EPA, in its test plan comments, responding to stakeholder comments on these test plans (including petitioner's), because it is the Challenge sponsor's responsibility to consider all comments on their test plans. For another example, EPA is not involved in developing categories of chemicals under the voluntary HPV Challenge Program, which again is the responsibility of the Challenge sponsors.

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[12] Comments on test plans are posted on EPA's website at www.epa.gov/opptintr/chemrtk/viewsrch.htm and www.epa.gov/chemrtk/hpvrstp.htm.

[13] The not infrequent disagreements between petitioner and EPA regarding the proper interpretation and application of some of the voluntary HPV Challenge Program animal welfare principles to individual test plans is noted in section IV. of this response document as underscoring one reason that these generally worded principles are not appropriate for codification as a rule.

[14] Examples of such prior correspondence in which EPA provided explanations in response to petitioner's criticisms of individual test plans include: letters dated December 19, 2002, and January 16, 2004, from Charles Auer, Director of EPA's Office of Pollution Prevention and Toxics, to Jessica Sandler, PETA's Federal Agency Liaison, and a February 25, 2005, letter from Charles Auer to Susan L. Hall, PETA's Legal Counsel.

Further, in Attachment II to this response document, EPA provides several examples highlighting how case-specific criticisms in the petition are invalid or inaccurate. For example, in one case (benzenmethanethiol), the petitioner criticized EPA for rejecting use of existing data on an alleged analogue chemical to avoid the need for new reproductive-developmental toxicity test. However, in EPA's scientific judgment, the proposed analogue belongs to a different chemical class than the sponsored substance and the resemblance is extremely superficial in terms of their biochemical characteristics.

In another example (2-vinylpyridine), the petitioner criticized EPA for seeking systemic toxicity testing on a corrosive chemical. However, in this case, the test chemical has been shown in other studies to exhibit systemic toxicity that does not follow the pattern of classic acids and bases that are typically subject to concerns regarding corrosivity. Furthermore, in this case, the Agency is recommending the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (40 CFR 799.9365, OECD 422) which is generally viewed as being consistent with the voluntary HPV Challenge Program animal welfare principles.

Attachment III to this petition response provides a selection of additional examples of EPA comments on HPV test plans where EPA's comments clearly promote the voluntary HPV Challenge Program animal welfare principles by suggesting to the Challenge sponsor changes from what the sponsor originally proposed. Examples include recommending *in vitro* rather than *in vivo* genetic toxicity studies, recommending the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (40 CFR 799.9365, OECD 422), and recommending reliance on SAR analysis rather than new testing.

E. Testing Alternatives

EPA has been actively participating in development of testing alternatives and revisions that promote animal welfare. EPA has repeatedly stated its commitment to a "reduction, replacement, refinement" strategy, consistent with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Authorization Act. 42 U.S.C. § 2851 *et seq*. "Where testing must be conducted to develop adequate data, the Agency is committed to reducing the number of animals used for testing, to replacing test methods requiring animals with alternative test methods when acceptable alternative methods are available, and to refining existing test methods to optimize animal use when there is no substitute for animal testing." 65 FR 81666 and 81691.

EPA is an active participant with several organizations involved in development of alternatives to animal testing, including ICCVAM, the Organization for Economic Cooperation and Development (OECD), and the Johns Hopkins University Center for Alternatives to Animal Testing (CAAT). As part of these efforts, the Agency has significantly contributed to establishing the acceptability of alternative methods, including, e.g., working with OECD to develop and accept the Acute Oral Toxicity – Up-and-Down Procedure (OECD TG 425), Acute Oral Toxicity – Fixed Dose Procedure (OECD TG 420), and the Acute Oral Toxicity – Acute

Toxic Class Method (OECD TG 423) as alternatives to the LD50 study. Additionally, EPA's Office of Research and Development (ORD) is conducting research under its Computational Toxicology initiative that will advance efforts to reduce animal use in regulatory testing.

As discussed in EPA's Federal Register notices associated with the voluntary HPV Challenge Program and proposed TSCA § 4 HPV SIDS test rule[15], and as noted by petitioner in its petition (see page 4), EPA has taken specific actions to promote alternative testing approaches specifically for animal welfare purposes. EPA dropped its preference for *in vivo* micronucleus genotoxicity testing and to accept either *in vivo* or *in vitro* studies (as allowed by OECD). In its voluntary HPV Challenge Program and TSCA § 4 HPV SIDS test rules, EPA encourages use of the *in vitro* Mammalian Chromosome Aberration Test method (40 CFR 799.9537, OECD 473) and urges companies to submit justifications if they elect to use the *in vivo* method. For Challenge sponsors participating in the voluntary HPV Challenge Program, these justifications of alternative testing should be submitted in the test plans. For testing that would be conducted pursuant to the proposed TSCA § 4 HPV SIDS test rule, EPA has proposed that these justifications must be submitted in the final study reports. Similarly, EPA is encouraging use of the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (40 CFR 799.9365, OECD 422), and urging Challenge sponsors to submit a rationale if they propose using both the Reproduction/Developmental Toxicity Screening Test (40 CFR 799.9355, OECD 421) and the Repeated Dose 28-day Oral Toxicity Study (40 CFR 799.9305, OECD 407) instead of the combined study. Again, for the voluntary HPV Challenge Program, these justifications should be submitted in the test plans, and for the TSCA § 4 HPV SIDS test rule, EPA has proposed that these justifications must be submitted in the final study reports.

Also, EPA is discouraging the conduct of acute aquatic toxicity testing of HPV Challenge Program chemicals with high octanol/water partition coefficients (i.e., log Kow values of 4.2 or greater) by indicating in the voluntary HPV Challenge Program that sponsors of such chemicals who believe that acute aquatic toxicity testing is appropriate should provide their rationale in their test plans. Chemical substances that are dispersible in water (e.g., surfactants, detergents, aliphatic amines, and cationic dyes) may have log Kow values of 4.2 or greater and may still be acutely toxic to aquatic organisms. To deal with such chemicals in the proposed TSCA § 4 HPV SIDS test rule, EPA proposed, as one alternative, that test sponsors who wish to conduct acute toxicity studies on chemicals with a log Kow value greater than or equal to 4.2 submit to EPA for approval a written request to conduct such studies prior to (e.g., 90 days) initiating such studies. EPA solicited public comment in its TSCA § 4 HPV SIDS proposed rule on this approach as well as other alternative approaches in this area. See 65 FR 81670.

In April 1999, several EPA personnel gave presentations at a workshop organized by the Johns Hopkins University Center for Alternatives to Animal Testing. The subject of the meeting was "TestSmart, an efficient and humane approach to collecting SIDS data for the voluntary

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[15] See 65 FR 81669 – 816970, 81684-81685, 81695 – 81697, Dec. 26, 2000.

HPV Challenge Program." Charles Auer, then Director of EPA's Chemical Control Division, gave a presentation that focused heavily on animal welfare aspects of the voluntary HPV Challenge Program.

In September 2001, the ICCVAM recommended that *in vitro* cytotoxicity test methods be considered as a tool for estimating starting doses for *in vivo* acute systemic toxicity testing studies (66 FR 49686-49687, September 28, 2001.) The recommendations were based on the Report of the International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity (ICCVAM, 2001a). The Guidance Document on Using In Vitro Data to Estimate In Vivo Starting Doses for Acute Toxicity (ICCVAM, 2001b) was also made available at that time. The guidance document provided standard operating procedures for two cytotoxicity test methods and instructions for using these assays to estimate starting doses for *in vivo* testing. Federal agency responses to the ICCVAM test method recommendations were announced on March 10, 2004 (69 FR 11448-11449). Federal agencies agreed to encourage, to the extent applicable, the use of in vitro tests for determining starting doses for acute systemic toxicity testing. EPA developed and issued a guidance document specifically encouraging those participating in the HPV Challenge Program to consider using the recommended *in vitro* tests as a supplemental component in conducting any new in vivo acute oral toxicity studies for the Program (www.epa.gov/chemrtk/toxprtow.htm).

In December 2002, EPA announced revised test guidelines for acute oral toxicity (OPPTS 870.1100) to enhance animal welfare while providing essential data needed to ensure protection of human health. www.epa.gov/chemrtk/toxprtcl.htm**,** 67 FR 77064, Dec. 16, 2002, and 68 FR 14635, March 26, 2003. The revised acute oral toxicity "Up-and-Down Procedure," which requires fewer animals, replaces the traditional Acute Oral Toxicity test guideline (LD50 study).

In sum, EPA has taken numerous concrete actions that promote the voluntary HPV Challenge Program animal welfare principles. When these serious efforts are considered in combination with the sound legal, policy, and procedural reasons for denying this petition, EPA's commitment to animal welfare is irrefutable.

F. Evidence of Success

An October 12, 2001, "Status Report on the High Production Volume (HPV) Challenge Program" examined the first 46 test plans posted on EPA's HPV website.[16] The report concluded that "sponsors have made maximum use of the guidance concerning the use of SAR and category proposals, and in combination with the significant amount of unpublished data

[16] This October 2001 HPV Status Report is posted at www.epa.gov/chemrtk/hpvstat.htm. EPA provided a copy to petitioner as an enclosure to an October 30, 2001, letter from Stephen L. Johnson, then Acting Administrator of EPA's Office of Prevention, Pesticides and Toxics, to Jessica Sandler, PETA's Federal Agency Liaison.

made available through the robust summaries, only a minimal amount of [new] testing has been proposed.. . . [T]he overall amount of proposed [new] testing is less than 10 percent." Id. "Sponsors are using category approaches, SAR, and other estimation techniques to reduce costs and the need for new testing. The net result is that new testing is being proposed for about six percent of the health and ecological endpoints, due in large part to the amount of test data, particularly unpublished data, brought forward."[17]

EPA's more extensive November 2004 HPV Status Report[18] covering 353 test plans submitted by July 2004 continues to confirm the findings of the earlier report. It provides factual statistical information demonstrating that a very substantial portion of the identified data needs can and have been filled via existing data and SAR rather than new testing. The "Endpoint Data Sources" table on pages 8 and 44 shows that "New testing has been proposed for fewer than 10% of the chemicals' endpoints."[19] The table shows further that, depending on endpoint, between 50 and 62 percent of the data have come from existing data, and 31 to 44 percent of the data have come from SAR and similar techniques. The report notes that "81% of all chemicals addressed in test plans have been included in a category."[20] These numbers demonstrate that the Agency's efforts to communicate and realize implementation of the voluntary HPV Challenge Program animal welfare principles have, in fact, been highly successful.

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[17] The October 2001 HPV Status Report noted that, in a few cases, "sponsors were not adequately explaining why they were proposing tests that were beyond the base set of screening tests and/or were not consistent with EPA's [October 14, 1999] guidance" and "it would be helpful for submitters to explain the rationale for any testing that is proposed beyond the SIDS endpoints" (for example, this could be intended to satisfy non-US testing requirements). As noted below in sections IV.E.6. and IV.F.6., EPA has taken steps to urge sponsors to submit their rationale for pursuing testing that deviates from the voluntary HPV Challenge Program animal welfare principles, including urging submission of such rationale with test plans.

[18] *Status and Future Directions of the High Production Volume Challenge Program*, EPA-743-R-04-001, Nov. 2004.

[19] The listed endpoints are fate, physical chemical properties, human health, and ecotoxicity.

[20] "As of July 2004, of the 353 submitted test plans, 114 contain category proposals covering 1,027 chemicals. These 1,027 chemicals represent 81% of the chemicals addressed by test plans." Nov. 2004 HPV Status Report, p. 45.

IV. Petition Response

A. Summary of Rationale

EPA is denying the petition for the reasons detailed below. These can be summarized as follows:

(1) Petitioner's criticisms notwithstanding, evidence shows that these principles have provided effective guidance to voluntary HPV Challenge Program sponsors and EPA, and have been highly effective in minimizing animal testing under the Program.

(2) In other contexts, EPA effectively factors in concerns about animal welfare in practice as EPA solicits existing test data, often pursuant to a statutory requirement.

(3) It is doubtful that EPA can require sponsors in the voluntary HPV Challenge Program to adhere to the Program's animal welfare principles.

(4) Companies are often motivated by financial considerations to adhere to many of the principles that reduce new animal testing in order to reduce expenditures.

(5) Though EPA believes in the "reduction, replacement, refinement" strategy for animal testing and works towards that end, the primary mission and statutory mandate under TSCA is to gather and assess data pertaining to the effects of chemical substances and mixtures on health and the environment and to regulate where appropriate to prevent unreasonable risk of injury to health and the environment. Implementation of other goals, however desirable, must be approached in a manner that does not jeopardize the statutory mandate. TSCA authorizes animal tests and says nothing about animal welfare.

(6) The animal welfare principles in the October 14, 1999, letter are intentionally phrased in general terms that do not easily lend themselves to rulemaking.

(7) The principles were developed as guidance for HPV SIDS screening level testing and may not apply in other contexts, so EPA needs to retain case-specific flexibility for future situations.

B. Applicability of TSCA § 21

The petition states that it is submitted under § 21 of TSCA (15 U.S.C. § 2620). Petition at 1. Although EPA believes that a petition requesting a generic animal welfare rule is not authorized by § 21, the Agency is nonetheless responding to the petition in 90 days, as requested by the petitioner.

Section 21(a) provides in part that a person may petition EPA "to initiate a proceeding for the issuance, amendment, or repeal of a rule under section 2603 [i.e., TSCA § 4] . . . of this title." 15 U.S.C. § 2620(a). Notwithstanding the references in § 21 to § 4 generally, EPA believes that § 21 is properly interpreted to apply only to chemical-specific legislative rules that have been or could be issued under the authority of § 4(a) (i.e., § 4 test rules). To adopt a broader interpretation would lead to internal inconsistencies within § 21. In particular, § 21(b)(4)(B) provides for *de novo* review of an EPA denial of a petition for the issuance of a new rule under § 4. To succeed in such a proceeding, the petitioner must demonstrate by a preponderance of the evidence that:

> (I) information available to the Administrator is insufficient to permit a reasoned evaluation of the health and environmental effects of *the chemical substance to be subject to such rule*. . .; and
>
> (II) in the absence of such information, *the substance* may present an unreasonable risk to heath or the environment, or *the substance* is or will be produced in substantial quantities and it enters or may reasonably be anticipated to enter the environment in substantial quantities or there is or may be significant or substantial human exposure to it.

15 U.S.C. § 2621(b)(4)(B)(i) (emphasis supplied). By its terms, § 21(b)(4)(B) can only apply to review of EPA denials of petitions to issue new chemical substance-specific rules, such as § 4 test rules. The factors that the court must consider in this *de novo* proceeding have no relevance when the petitioner's requested rule does not pertain to specific chemical substances or mixtures,[21] and Congress could thus not have intended that they apply. Moreover, these factors

[21] For example, § 4 authorizes EPA to promulgate rules providing for fair and equitable reimbursement from manufacturers and/or processors who are granted exemptions from test rule requirements to manufacturers and/or processors who actually conduct the testing. 15 U.S.C. §§ 2603(c)(3)(A), (4)(A). Under petitioner's reasoning, a denial of a petition for a new

are nearly identical to certain findings that EPA must make when it issues a § 4 test rule on its own initiative. See 15 U.S.C. § 2603(a).

This interpretation of § 21 makes sense from a policy perspective. EPA believes that Congress enacted § 21 in order to ensure expedited consideration of petitions related to chemical-specific rulemakings, in view of the potentially urgent need for EPA to address chemical risk issues and the direct and immediate impacts such rules have.

C. Lack of Statutory Mandate regarding Animal Welfare

Congress enacted the Toxic Substances Control Act (TSCA) in 1976 with "the primary purpose of this Act to assure that ... chemical substances and mixtures do not present an unreasonable risk of injury to health or the environment." 15 U.S.C. § 2601(b)(3). Toward that end, Congress declared it the policy of the United States that "adequate data should be developed with respect to the effect of chemical substances and mixtures on health and the environment," 15 U.S.C. § 2601(b)(1), and that "adequate authority should exist to regulate chemical substances and mixtures which present an unreasonable risk of injury to health or the environment. . ." 15 U.S.C. § 2601(b)(2). To promote those statutory purposes, Congress included in TSCA specific provisions authorizing EPA to require chemical testing and regulate to protect against potential unreasonable risks.

The primary section of TSCA concerning testing of chemical substances is § 4. TSCA § 4(b)(2)(A) specifically authorizes "whole animal tests" as an acceptable test methodolgy, and § 4(b)(1) says that "In determining the standards [for development of test data] . . ., the Administrator's considerations shall include the relative costs ... and the reasonably foreseeable availability of the facilities and personnel . . ." TSCA does not address animal welfare.

Consistent with the National Institutes of Health Revitalization Act of 1993 and the ICCVAM Authorization Act, the Agency has pursued a "reduction, refinement, replacement" strategy, which EPA views as appropriate and successful. Ultimately, EPA is handling animal welfare issues in a manner consistent with its relevant mandates and the congressional statement of policy in TSCA § 2(b) to develop adequate data with respect to the effect of chemical substances and mixtures on health and the environment in order to assure that chemical

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reimbursement rule would entitle a petition to *de novo* review under § 21(b)(4)(B). However, the factual demonstrations a petitioner is required to make in a *de novo* proceeding could not be reconciled with a review of fair and equitable reimbursement. Thus petitioner's assumption—that any rule or guidance issued pursuant to TSCA § 4 is subject to petition under § 21—renders § 21's *de novo* review provision nonsensical.

substances and mixtures do not present an unreasonable risk of injury to health or the environment. As elaborated below, EPA does not believe that the rulemaking requested by petitioner is necessary.

C. Voluntary HPV Challenge Program

The purpose of the voluntary HPV Challenge Program is to gather data on chemicals manufactured in large volumes and make those data publicly available.[22] This purpose is achieved through a voluntary commitment by companies to search for existing data or develop new data. Although EPA coordinates the voluntary HPV Challenge Program, EPA is not in a position to dictate to sponsors in a voluntary Program. When a sponsor submits a test plan, EPA, concurrently with other commenters, provides comments on the test plan to the sponsor. Although EPA desires that sponsors' participation be guided by the animal welfare principles in the October 14, 1999, letter, and the Agency's comments are often informed by these principles, EPA has never assumed the responsibility of ensuring that sponsors adhere to these principles, nor could it. Thus, test plan comments from the petitioner and other stakeholders are directed to the Challenge sponsor, not to EPA.

Consistent with this, it is doubtful that EPA has authority to promulgate rules to enforce the animal welfare principles within the voluntary HPV Challenge program, because no authority within TSCA or elsewhere requires that Challenge sponsors or other manufacturers and processors of HPV chemicals participate in the program or that they adhere to the guidelines in the Program. TSCA § 4 requires testing where EPA has made the requisite findings, and contains provisions regarding test standards. But § 4 does not apply to a voluntary program not based on § 4 findings, and thus conveys no authority to require that testing in a non-section 4 program proceed in a specified fashion. Nor do other sections of TSCA, nor any other statutory authority of which EPA is aware, bind the voluntary HPV Challenge Program sponsors to specific testing procedures.

Even assuming EPA has authority to promulgate the rule requested by petitioner, the Agency does not believe it is necessary or appropriate to do so. For example, as shown by the statistical evidence in section III.F. above, the voluntary HPV Challenge Program animal welfare

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[22] Though the voluntary HPV Challenge Program is not a TSCA regulatory program, its goals are consistent with one of the major policies of the statute, set forth at TSCA § 2(b)(1), that "adequate data should be developed with respect to the effect of chemical substances and mixtures on health and the environment and that the development of such data should be the responsibility of those who manufacture and those who process such chemical substances and mixtures." Among the test methodologies specifically sanctioned by TSCA is "whole animal tests." TSCA § 4(b)(2)(A).

principles have in fact motivated the chemical industry to make public large amounts of existing data that were previously unavailable, thus reducing the need to conduct new testing in many instances. Those numbers demonstrate that the Agency's efforts to communicate and realize implementation of the voluntary HPV Challenge Program animal welfare principles have, in fact, been highly successful.

It is not surprising that sponsors have operated consistently with these principles, since it is generally less expensive to identify and submit existing data and to utilize SAR and category approaches than to conduct new testing. The estimated cost of completing the full suite of HPV SIDS testing (in 2003 dollars) is $288,568.[23] The Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (40 CFR 799.9365, OECD 422), for example, is estimated to cost $113,977.

Thus, even assuming EPA could promulgate the requested rules, it would not be an effective or prudent use of EPA's limited resources, given that the principles have operated effectively as guidance and that the requested rule would not advance the Agency's mandate under TSCA.

D. TSCA § 4 HPV SIDS Test Rules

1. General

In the context of TSCA § 4 HPV SIDS test rules, EPA has committed to adopt approaches that are consistent with the voluntary HPV Challenge Program animal welfare principles that originated in the voluntary HPV Challenge Program. The Agency's October 14, 1999, letter committed to proceeding with TSCA § 4 HPV SIDS test rules in a manner consistent with the voluntary HPV Challenge Program animal welfare principles contained within the letter, and EPA has reiterated this commitment in subsequent letters and HPV *Federal Register* notices.[24] Due to inherent differences between the voluntary HPV Challenge Program and TSCA § 4 rulemaking procedures (per 40 CFR part 790), the voluntary HPV Challenge Program

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[23] Supporting Statement for a Request for OMB Review under the Paperwork Reduction Act, EPA ICR #1139.07 (January 25, 2005).

[24] 65 FR 81666 and 81691. March 15, 2000, letter from Susan H. Wayland, EPA's Acting Assistant Administrator for Prevention, Pesticides and Toxics, to Senator Bob Smith. See also footnote 13.

animal welfare principles in the October 14, 1999, letter have had to be adapted to the exigencies of testing via rule. The following discussion explains how EPA is applying these principles in the current TSCA § 4 HPV SIDS test rule (and intends to in future TSCA § 4 HPV SIDS test rules).

In sum, EPA concludes that promulgation of the rules requested by the petition, even assuming they are authorized under TSCA § 4,[25] would be an unnecessary and unproductive use of Agency resources. The Agency findings required under TSCA § 4 and EPA's commitments regarding HPV rulemaking help to ensure that animal welfare considerations are factored into TSCA § 4 HPV SIDS test rules. Further, the petitioners will have the opportunity to comment on any individual TSCA § 4 HPV SIDS test rules (and have done so extensively on the proposed HPV test rule), and any such rules will be subject to judicial review. In addition, it should be noted that, even if EPA were to issue the requested rules, the Agency always has authority to later modify those rules as applied in subsequent rulemaking, so the requested rules would not bind EPA in this regard.

2. Maximizing the Use of Existing Data and Analogue Data

Several of the voluntary HPV Challenge Program animal welfare principles involve the idea that certain testing may be unnecessary due to the availability of existing data on the specific chemical, or closely related "analogue" substances, often referred to as categories or Structure Activity Relationship (SAR) analysis.

In order to promulgate any test rules under § 4 of TSCA, the Agency must make certain findings stipulated in the statute. Among those findings, EPA must find that there are "insufficient data and experience upon which the effects of such manufacture, distribution in commerce, processing, use, or disposal of such substance or mixture or of any combination of such activities on health or the environment can reasonably be determined or predicted" and that "testing of such substance or mixture with respect to such effects is necessary to develop such data."[26] With respect to any substance for which sufficient data already exist, EPA would be unable to make these statutorily required findings for promulgation of a test rule. Therefore, by statute, EPA will not require unnecessary testing in TSCA § 4 HPV SIDS test rules nor in any other test rules.

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[25] EPA has authority under TSCA § 4(b)(1) to issue "standards for the development of test data."

[26] TSCA § 4(a)(1)(A)(ii) and (iii) and § 4(a)(1)(B)(ii) and (iii), see also the related discussion for the proposed TSCA § 4 HPV SIDS test rule at 65 FR 81664 – 81665 and 81667 – 81668.

EPA has indicated in the Federal Register notices describing the Voluntary HPV Challenge Program and proposed TSCA § 4 HPV SIDS test rule that these efforts are "designed to make maximum use of scientifically adequate existing test data and to avoid unnecessary, duplicative testing, thereby avoiding the excessive use of animal testing. If at any time, including after this rule is finalized, the Agency receives adequate existing data that fulfill a specific data gap, EPA will ensure that unnecessary testing is not conducted." 65 FR 81664, section F., see also 65 FR 81690, section D. Further, EPA noted that for certain "well-tested chemicals" SIDS level testing "would not further our understanding of the chemicals' properties" and is not warranted. 65 FR 81689. EPA does not intend to promulgate a TSCA § 4 rule mandating SIDS testing for such chemicals.[27]

In addition, many of the voluntary HPV Challenge Program animal welfare principles are intentionally worded generally such that it would be difficult to promulgate them as enforceable standards. These include the principles that say "[i]n analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach," "maximize the use of existing and scientifically adequate data," or "maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships." This is not a defect in the principles; rather it reflects EPA's intent that they serve as non-binding, flexible guidance for promotion of animal welfare in the voluntary HPV Challenge Program, and to the extent applicable, in TSCA § 4 HPV SIDS test rules. In fact, the subjectivity of these generally worded voluntary HPV Challenge Program animal welfare principles and how they apply to individual situations is underscored by the numerous differing interpretations that EPA and the petitioner apply to individual test plans submitted for the voluntary HPV Challenge Program.[28]

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[27] See, e.g., *Fact Sheet on Animal Welfare*, EPA 745-F-99-003 (July 2000), page 1 at www.epa.gov/chemrtk/anfacs2.pdf ("Chemicals for which adequate SIDS data already exist will not be retested under the HPV Challenge Program or any associated test rule(s) that are limited to SIDS testing.")

[28] EPA has noted these conflicting interpretations in several letters to petitioner: "We appreciate the time and effort that PETA and PCRM [Physicians Committee for Responsible Medicine] are committing to the development of comments on the test plans submitted under the HPV Challenge Program. EPA also spends considerable time and effort on the review of these test plans. In fact, on occasion, our reviews have identified similar issues associated with a test plan. However, the primary goal of this program is to identify critical gaps in publicly available information and to fill those gaps, when they exist, with appropriate data, based on the OECD's internationally agreed upon SIDS testing menu. While we recognize your desire that this be handled in every instance without the use of animal testing, at the present time, this is not possible. Based on our differing positions on this issue, it is clear that coming to agreement on those test plans that propose new animal testing to fill these critical data gaps will be very difficult." May 31, 2002, letter from William H. Sanders III, Director of EPA's Office of Pollution Prevention and Toxics, to Jessica Sandler, PETA's Federal Agency Liaison. "As we

As stated elsewhere, EPA intends that any TSCA § 4 HPV SIDS test rules will be consistent with the voluntary HPV Challenge Program animal welfare principles, to the extent applicable. For example, the first proposed TSCA § 4 HPV SIDS test rule (65 FR 81665 and 81668) did not include any chemicals that are Generally Recognized as Safe (GRAS) for a particular use by the Food and Drug Administration (FDA). This will allow additional time to determine the adequacy of existing data for those chemicals. However, these GRAS chemicals may be included in a future HPV SIDS test rule where data needs remain.

3. Terrestrial and Dermal Tests

Consistent with the voluntary HPV Challenge Program animal welfare principles, no terrestrial or dermal tests are included in EPA's proposed TSCA § 4 HPV SIDS test rule.

4. Reduced Testing on Closed System Intermediates

Consistent with the voluntary HPV Challenge Program animal welfare principles, the Agency has committed to a policy in the Voluntary HPV Challenge Program and in TSCA § 4 HPV SIDS test rules that "closed system intermediates" (as described by the OECD/SIDS guidelines) are eligible for a reduction in testing. 65 FR 81671 and 81695. Specifically, the reduced testing consists of the SIDS battery minus the tests for repeated dose toxicity and reproductive toxicity but including a developmental toxicity test. In the Federal Register notice for the proposed TSCA § 4 HPV SIDS test rule, EPA requested commenters to identify chemicals which qualify as closed system intermediates. Id.

5. 120 Days between Posting Test Plan and Testing

Consistent with the voluntary HPV Challenge Program animal welfare principles, EPA is providing a 120 day period to comment on both test plans in the voluntary HPV Challenge Program, as well as on the TSCA § 4 HPV SIDS proposed test rules. Among other things, this

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have stated before, the Agency is committed to ensuring that the animal welfare principles outlined in the October 14, 1999, letter to HPV Challenge participants are being followed and that sincere efforts are made to reduce and avoid the use of animal testing. As you know, there have been numerous test plans where we reached the same conclusion in our comments after careful consideration and there have been others where we did not. In all instances, however, the Agency has made every effort to ensure that unnecessary testing is avoided." January 16, 2004, letter from Charles Auer, Director of EPA's Office of Pollution Prevention and Toxics, to Jessica Sandler, PETA's Federal Agency Liaison.

provides an opportunity to identify situations where adequate data already exist. For the first proposed TSCA § 4 HPV SIDS test rule (65 FR 81658), EPA allowed a 120-day comment period (twice the usual 60-day comment period) to mirror the 120-day public comment period for the review of test plans under the voluntary HPV Challenge Program. The Agency intends that all TSCA § 4 HPV SIDS test rules will provide this 120 day comment period on the proposed rule. See 65 FR 81690. EPA's designation in the proposed test rule of the tests and test methods to be required for each chemical is equivalent to the "test plan" in the voluntary HPV Challenge Program. The rulemaking process provides the public with ample notice of chemical testing requirements sufficiently in advance of the initiation of testing to allow the public to conduct searches for existing data, submit data to EPA, comment on testing requirements and methods, and prevent unnecessary and duplicative testing.

6. Submission of Rationales for Conducting Certain Testing

The petition (p. 4) notes that EPA's December 26, 2000, Federal Register notice on the voluntary HPV Challenge Program (65 FR 81686) "expanded on several items" beyond the animal welfare principles articulated in EPA's October 14, 1999, letter to voluntary HPV Challenge Program participants. These provisions, extracted from the December 26, 2000, Federal Register notice on the voluntary HPV Challenge Program, pertain to EPA encouraging Challenge sponsors to submit justifications if they propose to pursue certain testing. As discussed in EPA's Federal Register notices associated with the voluntary HPV Challenge Program and proposed TSCA § 4 HPV SIDS test rule[29], and as noted by petitioner in its petition (p.4), EPA has taken specific actions to promote alternative testing approaches specifically for animal welfare purposes. For testing conducted pursuant to the proposed TSCA § 4 HPV SIDS test rule, EPA encourages use of the *in vitro* Mammalian Chromosome Aberration Test method (40 CFR 799.9537, OECD 473) and requires companies to submit justifications in their final study reports if they elect to use the *in vivo* method. Similarly, EPA is encouraging use of the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (40 CFR 799.9365, OECD 422), and proposed to require test sponsors to submit a rationale in their final study reports if they use both the Reproduction/Developmental Toxicity Screening Test (40 CFR 799.9355, OECD 421) and the Repeated Dose 28-day Oral Toxicity Study (40 CFR 799.9305, OECD 407) instead of the combined study.

Also, EPA is discouraging the conduct of acute aquatic toxicity testing of HPV chemicals with a high log K_{ow} (4.2 or greater). Chemical substances that are dispersible in water (e.g., surfactants, detergents, aliphatic amines, and cationic dyes) may have log K_{OW} values greater than 4.2 and may still be acutely toxic to aquatic organisms. To deal with such chemicals, EPA recommended in the proposed HPV test rule that Challenge sponsors who wish to conduct acute toxicity studies on chemicals with a log K_{OW} greater than or equal to 4.2 submit to EPA for

[29] See 65 FR 81669 – 816970, 81684-81685, 81695 – 81697, Dec. 26, 2000.

approval a written request to conduct such studies 90 days prior to conducting such studies. EPA solicited public comment on this approach as well as other alternative approaches in this area, but did not receive comments (including from petitioner). See 65 FR 81670.

E. Non-HPV Testing Requirements

1. General

EPA issues mandatory chemical testing requirements under several different authorities. These testing authorities include § 4 test rules (15 U.S.C. § 2603, 40 CFR Parts 790 - 799), § 4 Enforceable Consent Agreements (15 U.S.C. § 2603, 40 CFR Parts 790 - 799), and § 5(e) Consent Orders (15 U.S.C. § 2604(e)). In the following discussion, these regulatory testing requirements will often be referred to generically as "TSCA testing requirements" or "mandatory TSCA testing."

As noted above, EPA believes that financial cost savings will motivate compliance with the voluntary HPV Challenge Program animal welfare principles, such as avoidance of new testing, even absent any legal mandate to do so. While EPA is committed to promoting animal welfare, EPA does not believe the voluntary HPV Challenge Program animal welfare principles, as a whole, would be appropriate as a mandatory rule that would apply to all TSCA testing requirements. As noted, these animal welfare principles were developed in the specific context of the voluntary HPV Challenge program involving OECD's Screening Information Data Set (SIDS). The principles are tailored specifically for SIDS screening level testing, and may not be appropriate for other kinds of testing EPA might require under TSCA.

2. Maximizing the Use of Existing Data and Analogue Data

Several of the voluntary HPV Challenge Program animal welfare principles involve the idea that certain testing may be unnecessary due to the availability of existing data on the specific chemical, or closely related "analogue" substances, often referred to as categories or Structure Activity Relationship (SAR) analysis. EPA already avoids unnecessary testing where adequate data already exist by simply not requiring those tests.

As discussed above in section IV.E.2., EPA lacks legal authority to require testing under TSCA § 4 where sufficient data already exist. This is also true for the ability to issue orders under §5(e). Thus, where EPA determines that existing data is sufficient, EPA will ensure that unnecessary testing is not required. EPA will consider whether existing data suffices to obviate

the need for new testing at any time, even after a TSCA testing requirement is finalized.[30] See, e.g., 65 FR 81658, 81664, Dec. 26, 2000.

Again, as noted in section IV.E.2. above, many of the voluntary HPV Challenge Program animal welfare principles are worded generally and are not well suited to an enforceable standard. These include the principles that say "[i]n analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach," "maximize the use of existing and scientifically adequate data," or "maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships."

The test rule regulations at 40 CFR Part 790 already contain provisions in subpart E (§790.80 et. seq.) for exemptions from § 4 test rules based on the equivalence between a chemical for which exemption is sought and a chemical for which test data have been or are being submitted in accordance with a test rule. "*Equivalent* means that a chemical substance or mixture is able to represent or substitute for another in test or series of tests, and that the data from one substance can be used to make scientific and regulatory decisions concerning the other substance." §790.3.

Please note that in the TSCA §5 New Chemicals Program, analogue data already figure prominently and have done so for many years. EPA's hazard assessments for new chemicals are often based on analogue data. (See Chemical Categories Report at www.epa.gov/oppt/newchems/chemcat.htm and references for use of SAR.) Further, for §5(e) Consent Orders that require testing on a new chemical substance, if the Agency is presented with suitable surrogate/analogue data, EPA can and would consider the alternate data and modify or revoke the Consent Order requirements as appropriate based on the newly presented data.[31]

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[30] For example, EPA is now in the process of taking a direct final action to amend the final TSCA § 4 test rule, In Vitro Dermal Absorption Rate Testing of Certain Chemicals of Interest to the Occupational Safety and Health Administration (69 FR 22402, April 26, 2004), by removing the requirements that testing be conducted to determine permeability constants (Kp) for methyl isoamyl ketone (CAS No. 110-12-3) and dipropylene glycol methyl ether (CAS No. 34590-94-8). EPA is basing its decision to revoke these testing requirements on information it received after publication of the final rule. EPA has determined that these existing data satisfy the testing needs identified in the test rule so that conducting these test is no longer necessary.

[31] For example, EPA revoked a number of §5(e) Consent Orders on acrylates and methacrylates based on 2-year cancer bioassays on a few representative chemicals conducted under an agreement between the Agency and the Specialty Acrylates and Methacrylates (SAM) Panel of the Chemical Manufacturers Association (CMA, now the American Chemistry Council or ACC). Based on currently available information, EPA no longer considers such testing necessary on new chemical acrylates or methacrylates as a category based on health concerns.

Since §5(e) orders are authorized where "the information available to the Administrator is insufficient to permit a reasoned evaluation of the health and environmental effects of a chemical substance", the Agency is precluded from imposing an order where adequate data exist, including analogue data.

3. Terrestrial and Dermal Tests

Some of the voluntary HPV Challenge Program animal welfare principles state that certain types of tests should be avoided, specifically terrestrial toxicity testing and dermal toxicity testing. While EPA has dealt with this issue in the context of the voluntary HPV Challenge Program and TSCA § 4 HPV SIDS test rules (see 65 FR 81658, 81666, Dec. 26, 2000), the Agency cannot rule out the possibility that such testing might be necessary in other circumstances. Nor does the statute restrict the type of health or environmental effects testing which may be relevant to a determination as to whether a chemical substance may present an unreasonable risk (see TSCA § 4(b)(2)(A)).

4. Reduced Testing on Closed System Intermediates

Voluntary HPV Challenge Program participants were asked not to develop repeated dose and reproductive toxicity testing for closed system intermediates. The meaning of "closed system intermediates" in the voluntary HPV Challenge Program is the same as the OECD SIDS description. According to this description, a closed system intermediate is removed from the manufacturing equipment and may even be transported to other facilities. Recognizing that a closed system intermediate does have potential for exposure, the voluntary HPV Challenge Program does not completely exempt them, but rather includes certain animal testing for closed system intermediates, such as acute toxicity and genetic toxicity. For the same reason (i.e., potential exposures), EPA does not agree that repeated dose and reproductive toxicity testing for closed system intermediates would never be appropriate under TSCA.

5. 120 Days between Posting Test Plan and Testing

Voluntary HPV Challenge Program animal welfare principle number 9 says: "Companies

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See www.epa.gov/oppt/newchems/cat02.htm#Acrylates/Methacrylates.

will allow 120 days between the posting of test plans and the implementation of any testing."[32] While EPA has committed to providing a 120 day comment period on proposed TSCA § 4 HPV SIDS test rules, EPA is not willing to require a 120 day comment period for all TSCA testing requirements. Neither TSCA nor the Administrative Procedure Act (5 U.S.C. § 551 et. seq.) specify the duration of a minimum period for comment. EPA's standard comment period for non-HPV proposed § 4 test rules has been 60 days, although there are case-specific examples where EPA granted extensions or adopted different comment periods to meet the needs of the situation. EPA does not see the value and is unwilling to commit to a 120-day comment period across the board for all future non-HPV test rules. Mandating additional time for the public to comment on proposed test plans could unnecessarily prolong an already lengthy rulemaking process and delay moving forward to protect against unreasonable risks to human health and the environment. Moreover, timing may be urgent or different in certain cases. Thus, the Agency needs to retain case-specific flexibility for future non-HPV testing requirements.

6. Submission of Rationales for Conducting Certain Testing

The petition (p. 4) notes that EPA's December 26, 2000, Federal Register notice on the voluntary HPV Challenge Program (65 FR 81686) "expanded on several items" beyond the animal welfare principles articulated in EPA's October 14, 1999, letter to voluntary HPV Challenge Program participants. These provisions, extracted from the December 26, 2000, Federal Register notice on the voluntary HPV Challenge Program, pertain to EPA encouraging Challenge sponsors to submit justifications if they propose to pursue certain testing. Again, these tests include in vivo genotoxicity testing; separate Reproduction/Developmental Toxicity Screening Test (40 CFR 799.9355, OECD 421) and Repeated Dose 28-day Oral Toxicity Study (40 CFR 799.9305, OECD 407) instead of the Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (40 CFR 799.9365, OECD 422); and acute aquatic toxicity testing of HPV chemicals with a log K_{ow} of 4.2 or greater.

Section IV.E.6. above explains how the proposed TSCA § 4 HPV SIDS test rule will address these situations by requiring persons who conduct these tests to submit such rationales in their final study reports. However, in some future non-HPV test rules that go beyond basic SIDS testing, EPA may deem it necessary and appropriate to require those tests that are associated with submission of justifications under the voluntary HPV Challenge Program and TSCA § 4 HPV SIDS test rule. EPA, therefore, does not consider it appropriate to promulgate a rule that would limit agency discretion in this regard.

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[32] As discussed in section II.D.1. above, this principle is listed as number 9 in the petition, although it was number 10 in the Agency's October 14, 1999, letter to voluntary HPV Challenge Program participants.

IV. Conclusion

While EPA is committed to reducing, refining and replacing animal testing, for the aforementioned reasons, EPA continues to believe that the most reasonable, balanced and appropriate way to communicate and realize implementation of the objectives of the voluntary HPV Challenge Program animal welfare principles is as guidance, rather than as mandatory requirements. Therefore, the petition is denied.

ATTACHMENT II

Selected Rebuttals of Petitioner's Criticisms of EPA's Comments on HPV Test Plans

Petition Page: 8

Chemical: 2-hydroxy-4-n-octoxybenzophenone (CAS No. 1843-05-6)

Petition Criticism: "Cytec Industries and Ciba's test plan for '2-hydroxy-4-n-octoxybenzophenone' was posted in November 2001. It proposed no further testing. EPA, however, requested that a reproductive/developmental toxicity test be conducted, even though the company had submitted data for a study that evaluated reproductive and developmental toxicity over four generations of animals at a high dose level that should have been adequate to meet HPV screening requirements. Even though this test was not considered GLP, the HPV Program does not require GLP, and the vast majority of published data are not GLP. EPA's request ignored 'existing and scientifically adequate data' and exemplified check-the-box testing rather than a thoughtful approach to toxicology."

EPA Rebuttal: The reason EPA considered the existing data inadequate was related not to GLP, but rather to study design. EPA recommended an OECD TG 421 study because the sponsor's 4-generation study was conducted at only one dose level that showed no toxicity and was about one-third of the normal recommended limit dose (a limit dose is a high dose, usually 1000 mg/kg body weight/day, suggested in OECD guidelines that can be used as a single dose; if the study using a limit dose shows no observable toxic effects, then a full study using several doses may not be necessary). No explanation was given as to why only one dose at this level was chosen for the study. To obtain screening-level data, the study should be conducted using a limit dose, showing no toxicity, or at multiple dose levels with the highest dose resulting in toxicity.

Petition Page: 8

Chemical: Propylene Streams Category

Petition Criticism: "ACC's November 2001 test plan for the 'propylene streams' category proposed additional testing for developmental toxicity and *in vivo* genetic toxicity for propylene. In its public comments, the animal protection community pointed out the fact that these compounds are well-characterized and have clearly documented toxicological mechanisms, the most important of which is the fact that these compounds are rapidly expelled from the body. Despite the abundant existing information on their toxicity and metabolism—including extensive animal testing—EPA did not raise any concerns about the irrelevance of further testing of these compounds. This well-known information was corroborated by the results of the redundant

testing that was conducted on these compounds. Because EPA did not object to ACC's use of the separate developmental toxicity testing and *in vivo* genetic toxicity testing, at least 1,380 animals were killed to again demonstrate that a non-toxic substance was, in fact, non-toxic. Both the Sponsor and EPA flagrantly violated the animal welfare guidelines."

EPA Rebuttal: EPA commented as follows: "The submitter indicates that the data for HPV purposes are, or will become, available from other testing programs for the acute, genetic, repeated dose, reproductive, and developmental toxicity end points of propylene and propane. The submitter states that it will provide a technical narrative that evaluates the data from these other programs that are applicable to the propylene streams category...EPA will evaluate both the propylene and propane data after the propylene test plan has been submitted. The ultimate acceptability of the present category test plan depends on the acceptability of the referenced test plan." Thus, EPA withheld judgment on this category and petitioner's characterization of EPA's comments is inaccurate.

Petition Page: 9

Chemical: Tricresyl Phosphate (CAS No. 1330-78-5)

Original EPA Comments: "*Developmental Toxicity.* The submitter acknowledged a lack of developmental toxicity data and noted that testing is needed for this endpoint. EPA strongly recommends that the submitter conduct a developmental toxicity study according to OECD Guideline 414 because adverse effects on testes were observed in the reproduction studies and there is a concern for potential effects on the developing fetus."

Petition Criticism: "In November 2001, Great Lakes Chemical Corporation (GLCC) submitted a test plan for 'phosphoric acid tris (methylphenyl) ester (tricresyl phosphate),' which called for a developmental toxicity study. The test plan was extremely sloppy and lacked the necessary information on basic physiochemical properties. The animal protection community asked that EPA fulfill its role in proactively addressing the submission of such inadequate plans under the HPV Program. Nevertheless, EPA approved the testing. In violation of the guidance to minimize the number of animals used, EPA "strongly" recommended that an OECD 414 (1,300 animals) be conducted on this reproductive toxicant rather than (1) requesting that the combined reproductive/developmental toxicity test, which uses half the number of animals be used, and/or (2) recognizing that existing data show that this substance apparently interferes with reproduction. EPA also asked for fish toxicity testing and the sponsor complied with both demands. Despite repeated requests by the animal protection community spanning several years for an explanation of EPA's demand that an OECD 414 be conducted, EPA has never provided a response."

EPA Rebuttal: Multiple significant effects on both male and female reproductive organs in a

majority (or all) of the animals tested at certain doses were observed in repeated-dose or reproductive studies. Pup viability and litter size were also affected after TCP exposure. Because of the severity, high incidence, and nature of these effects, EPA believed it important to conduct a complete developmental study (OECD TG 414) for this compound to determine whether developmental effects might also be observed.

Petition Page: 9

Chemical: Fatty Nitrogen Derived Cationics Category

Petition Criticism: "In January 2002, ACC's test plan was posted for 'fatty nitrogen-derived cationics,' which did not call for any additional animal testing. In yet another example of check-the-box toxicology, EPA called for a reproductive/developmental toxicity test without apparently considering the results of two multigenerational reproduction studies that were referenced in the test plan, and which demonstrated no adverse reproductive effects. Further, the Sponsor provided developmental toxicity data for nine of the 13 chemicals in this category, none of which showed evidence of adverse developmental effects."

EPA Rebuttal : Although petitioner states that data were available from two multigeneration studies, these data were submitted for two analogs and not for the category members. One of the multigeneration studies could not be considered at all because the analog was not appropriate to represent the category members. Also, histopathology data on reproductive organs from subchronic studies were available for only two category members. Therefore, EPA recommended conducting a reproduction/developmental screening test (OECD Guideline 421) on one of the chemicals (CAS No. 68607-29-4) to represent the monoalkyl category members. In a category of thirteen substances, it is important to have adequate data to address adequately the basic screening level endpoints for the entire category.

Petition Page: 12

Chemical: (alkyl diphenyl oxide disulfonates) (ADPODS) category

Petition Criticism: "the test plan called for two repeated-dose/reproductive/developmental toxicity tests on two chemicals that were not part of the HPV Program."

"EPA agreed with the test plan even though the robust summaries contained no fewer that[n] 11 chronic and subchronic studies that examined reproductive organs, as well as a developmental study"

EPA Rebuttal: It is appropriate and encouraged to include non-HPV chemicals to strengthen the basis for the category. For a category, data are needed for enough members to show a trend or pattern, or an absence of effects. To address the developmental toxicity for the category, only

one test, of limited value, was submitted on a chemical at one end of the category range. Thus, the data were too limited to adequately address the endpoint for the category, and more data were needed to characterize the category.

Subchronic study data on reproductive organs in the absence of adequate developmental toxicity data are not sufficient to address the reproductive endpoint. EPA, therefore, recommended a combined reproductive/developmental toxicity screening test (OECD TG 421) which uses fewer animals than the submitter-proposed combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422).

Petition Page: 14

Chemical: Lubricating Oil Basestocks Category

Petition Criticism: "In April 2003, EPA posted API's test plan for the 'lubricating oil basestocks category,' which proposed a repeated-dose, reproductive, and developmental toxicity test and a reproductive/developmental toxicity test. API's proposal failed to provide any chemical analyses or characterizations of these materials, including basic compositional information. It also ignored existing data on the toxicology and hazards of petroleum fractions, which constitute the toxic components of this category, and failed to group these substances with similar substances such as API's own waxes and related substances category. Rather than request a more thorough and thoughtful analysis, EPA requested that several additional tests be conducted."

EPA Rebuttal: The test plan is on 36 complex petroleum streams, each containing up to hundreds of components. The sponsor characterized them in terms of molecular weight ranges, physicochemical characteristics and predominating structural components, such as naphthenic and paraffinic, and broke them down into three subcategories based on degree of processing. The petroleum fractions mentioned by petitioner may contribute to but do not account for or characterize the composition of these streams. The thoughtful strategy behind the sponsor's test plan was to test the hypothesis that the comparative toxicity and environmental behavior of these streams is based on the degree to which the streams have been processed to remove impurities, as well as their bioavailability as a function of molecular weight. The sponsor proposed testing representative streams within each subcategory to test this hypothesis, and EPA agreed, pointing out where certain tests appeared to be inadequate or where members selected for testing were not representative of the subcategory. It was understood that a good representative data set for each of the subcategories would preclude the need for testing other members of this very large category.

For health effects, EPA agreed with the sponsor's proposal for reproductive or developmental toxicity testing of representative members of two subcategories where no data existed but recommended the oral route rather than the sponsor's proposed dermal route. EPA also

proposed *in vitro* but not *in vivo* genotoxicity tests for representative streams because of inadequacies in the test data submitted. EPA also recommended a combined repeated dose and reproductive & developmental toxicity screen for a representative member of one of the subcategories because of inadequacies in the test data submitted, but offered the submitter the option of providing additional information on the submitted studies to render them adequate for the purposes of the HPV Challenge Program.

EPA made similar comments on other parts of the test plan, encouraging the sponsor to provide further study details or use data from other studies to meet HPV testing needs. For example, for ecological effects, EPA requested the submission of robust summaries or additional study details as an alternative to further testing wherever submitted data on the ecotox endpoints appeared to be inadequate for a representative of each of the subcategories.

Thus, the sponsor provided a thoughtful approach and EPA responded with a thoughtful, test-minimizing analysis of the test plan.

Petition Page: 18

Chemical: 2-vinylpyridine (CAS No. 100-69-6)

Petition Criticism: "The animal protection community objected strenuously to this plan as, according to the Sponsor, the substance is "corrosive to tissues, flammable, and acutely toxic by the oral and dermal routes." Its comments included the fact that "chemicals that are classified as irritating will not likely cause systemic toxicity at doses which do not also cause significant local gastrointestinal effects. All three cited repeated-dose studies shared this principle."

EPA Rebuttal: The voluntary HPV Challenge Program seeks to provide a reasonable set of screening information on the HPV chemicals. The Agency considers on a case-by-case basis all data provided in a submission. Every effort is made to use all existing information in a weight-of-evidence approach to avoid excessive testing recommendations, especially for endpoints such as acute toxicity. The Agency is, however, very concerned with filling major data gaps in the reproductive and developmental area, especially when there are data indicating a basis for such concern.

Concerns regarding testing of corrosive chemicals are generally associated with severity of the tissue response which either restricts further dosing, reduces the animal viability, or restricts feeding. A chemical with potential to be corrosive or reactive is reviewed from the perspective of concern for potential for low doses to be associated with reproductive or developmental toxicity versus the practicality of conducting longer term studies. When there is evidence that longer term testing is both practical and needed, such as in this case, where a 90-day repeated-dose study had been done using a corn oil vehicle, EPA recommends further testing–in this case the combined repro/developmental study to fill data gaps for reproductive and developmental toxicity–because it will provide data for the endpoints at minimal loss of animal life.

While reactive as a monomer, 2-vinylpyridine exhibits systemic toxicity (changes in organ weights including testes, alterations in hematological parameters...) that does not follow the pattern of classic acids or bases that are generally the focus of concern for corrosivity.

Petition Page: 19

Chemical: Benzenemethanethiol (benzyl mercaptan; CAS No. 100-53-8)

Petition Criticism: "The Sponsor proposed using existing data on a more acutely toxic analogue that also causes reproductive and developmental effects in animals in order to avoid conducting a new reproductive/developmental toxicity test on this substance. Despite this conservative and more protective approach, EPA rejected the use of the analogue and stated that a repeated-dose/reproductive/developmental toxicity test should be conducted (which uses 675 animals rather than the proposed test that would have used 40 animals). In its comments, posted almost eight months after the close of the public comment period, EPA ignored the animal welfare ramifications as well as thoughtful toxicology."

EPA Rebuttal: In its posted comments, EPA stated that "For human health, EPA does not consider phenyl mercaptan (thiophenol) appropriate for use as an analogue for benzyl mercaptan. The metabolic profiles of these chemicals are expected to be very different. Phenyl mercaptan is expected to be metabolized like a typical aromatic substrate while metabolism of benzyl mercaptan is likely to focus on the methanethiol group." EPA has stated from the outset of the program that the use of analogue data is acceptable where it is scientifically justified. The proposed analog belongs to a different chemical class than the sponsored substance and their structural resemblance is extremely superficial. To consider these substances analogous would violate fundamental chemistry and biochemistry principles and would not reflect "thoughtful toxicology." Therefore, the proposed analog may, in fact, not represent a conservative position and relevant data are needed.

ATTACHMENT III

Additional Examples of EPA Comments on HPV Test Plans that Promote the Voluntary HPV Challenge Program Animal Welfare Principles

Acute testing; In vivo genetic toxicity testing

Chemical: Isopropylated Triphenyl Phosphate

Summary: EPA recommended use of available data as alternative to conducting oral acute study.

EPA Comments: "Except for the dermal study, all the acute toxicity studies are inadequate. However, EPA believes that the submitter may be able to enhance the data on the acute oral toxicity endpoint by utilizing the dosing data from the 28-day repeat-dose study to estimate an acceptable LD50."

Chemical: 2,3-Dihydro-2,2-dimethyl-7-benzofuranol

Summary: The sponsor proposed to conduct an acute dermal toxicity study, an *in vivo* genotoxicity study and a combined repeat dose/reproductive/developmental toxicity study. EPA discouraged the acute dermal and *in vivo* tests.

EPA Comments: "Acute Toxicity. Acute dermal testing is not an element of the Challenge program. Although the acute inhalation toxicity study is considered inadequate, the existence of an adequate acute oral toxicity study is sufficient for this endpoint for the purposes of the U.S. HPV Challenge Program. Genotoxicity. EPA encourages conducting an *in vitro* genotoxicity study rather than an *in vivo* study unless the properties of the chemical indicate otherwise."

Chemical: Metal Carboxylates Category

Summary: EPA discouraged a proposed *in vivo* mutagenicity testing not part of Challenge Program.

EPA Comments: "The test plan indicates that chromosomal aberration testing is planned for cobalt neodecanoate; Table I implies that this will be an *in vivo* test, which is beyond the scope of the U.S. HPV Challenge Program. The plan included no rationale for conducting an *in vivo* study; the nature of the planned testing needs clarification."

Chemical: Isocyanic acid, m-phenylenediiso-propylidene

Summary: EPA discouraged unnecessary testing because adequate data already exist.

EPA Comments: "Adequate data are available for acute toxicity, repeated-dose toxicity, and gene mutation. The submitter plans to conduct tests for chromosomal aberrations and developmental toxicity but did not specify protocols. EPA recommends the OECD 473 (in vitro

cytogenetic assay) and 421 (combined reproductive/developmental toxicity) Guidelines."

Combined Repeated Dose Reproductive-Developmental Toxicity Testing

Chemical: Diphenyl Spiropentylphosphite

Summary: EPA recommended combined repeated dose reproductive-developmental toxicity test (OECD 422) instead of separate studies.

EPA Comments: "Proposed health endpoint testing: Developmental toxicity. The proposal includes conducting a combined repeat dose/reproductive/developmental toxicity screening test (OECD Test Guideline 422) in addition to a pre-natal developmental toxicity test (OECD 414). There is no rationale presented for conducting both tests. The OECD 422 screening study is sufficient to cover all three endpoints (repeat dose, reproductive and developmental toxicity) for the purposes of the U.S. HPV Challenge Program."

Chemical: Ethyl Dimethyl (aminoiminomethyl)methylcarbamate Hydrochloride

Summary: EPA encouraged combined study.

EPA Comments: "...EPA therefore reserves judgment on whether carbamate hydrochloride meets the criteria for a 'closed system intermediate,' pending the submission of additional information. Alternatively, the submitter may conduct a combined repeated-dose/reproductive/developmental toxicity screening test (OECD TG 422) instead of the proposed developmental toxicity study (OECD TG 414), which would then satisfy the repeated-dose and reproductive toxicity endpoints and obviate the need to sustain a 'closed system intermediate' claim."

Chemical: Alkyl (C12-14) Glycidyl Ether

Summary: EPA recommended reliance on existing data instead of a new reproductive study.

EPA Comments: "*Reproductive Toxicity.* Data are available for a 13-week repeated-dose dermal study in rats for which reproductive organs were examined histopathologically, and no adverse effects were observed. This study together with the adequate developmental toxicity study is considered adequate for the reproductive toxicity endpoint."

Chemical: Diallyl Oxydiethylene Dicarbonate

Summary: EPA recommended combined repeated dose reproductive-developmental study and referenced Challenge guidance on addressing reproductive effects without conducting a separate reproductive study.

EPA Comments: "*Repeated-dose toxicity*. ... EPA disagrees with the submitter's plan to evaluate toxicity to reproductive organs in the proposed 90-day repeated-dose study. This

approach is not adequate for the purposes of the HPV Challenge Program. EPA's HPV Challenge Guidance specifies that such an assessment of toxicity to reproductive organs is acceptable only in the case of an existing 90-day study when an acceptable developmental toxicity study is available. EPA recommends that the submitter conduct a Combined Repeated-dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD 422) to address this endpoint."

Chemical: 2-Chloropyridine

Summary: EPA recommended combined study.

EPA Comments: "EPA agrees that testing is needed for the repeated-dose, reproductive, and developmental toxicity endpoints. However, EPA recommends that the submitter conduct a combined repeated-dose/ reproductive/developmental toxicity screening test (OECD TG 422) rather than the proposed separate tests (OECD TGs 407 and 421)."

Chemical: Benzenesulfonic Acid

Summary: EPA recommend considering harsh chemical properties vis-a-vis further testing.

EPA Comments: "The submitted data for the acute and genetic toxicity endpoints are adequate for the purposes of the HPV Challenge Program. Although the submitter has proposed conducting a combined screening test to address repeated-dose, reproductive and developmental endpoints, based on the strong acidic and corrosive nature of the substance, EPA believes that the sponsor needs to consider whether the proposed testing would yield meaningful results. Therefore, the submitter needs to reconsider the testing proposal before conducting such studies and better characterize the corrosivity with available *in vitro* methods."

Chemical: Triisopropylborate

Summary: EPA recommended that analog data plus physical-chemical data could satisfy endpoint without further testing.

EPA Comments: "Adequate information was available for acute toxicity. No data were provided for repeated-dose, developmental and reproductive effects and a combined test addressing these endpoints (OECD TG 422) was proposed. However, if hydrolysis is sufficiently rapid at the physiologically important pH of 1.2 in the stability in water test, then data on the break-down products (isopropanol and boric acid) could be used to address these endpoints. Testing was proposed for assessing chromosomal aberrations (OECD TG 473). Information provided on the reverse mutation assay in *Salmonella typhimurium* was missing details concerning the conditions of the test and whether a closed-system was used. If volatility is more predominant than hydrolysis under the conditions of the test, then a closed-system approach is needed."

Use of ECOSAR Modeling for Ecotoxicity

Chemical: Dimethyl 3,3'-thiobispropionate

Summary: EPA acknowledged SAR would be acceptable to satisfy ecotox endpoint without testing (if measured data on analog is provided).

EPA Comments: "For all ecological endpoints, the submitter provided only estimated data using ECOSAR. In order to meet the guidelines of the HPV Challenge Program, the submitter needs to provide either measured data on the subject chemical or predicted SAR values plus measured data on an analogue."

Chemical: Rxn Pdct (Cyclododecanol/-anone/Nitric Acid), High-Boiling Frxn (Corfree (R) M1)

Summary: EPA accepted partial data plus ECOSAR to satisfy endpoint without further testing.

EPA Comments: "*Fish and Invertebrates.* The fish and daphnia acute toxicity tests were conducted with shorter (48-hour fish, 24-hour daphnia)) than required (96-hour fish, 48-hour daphnia) test durations. Although no new testing is proposed, EPA agrees with the submitter that this chemical is expected to show low toxicity based on measured data and the ECOSAR predicted values (>100 mg/L). The submitter, however, needs to provide model input parameters for the ECOSAR predictions."

Chemical: Ketoacids Category

Summary: EPA accepted analog data plus ECOSAR to satisfy endpoint without further testing.

EPA Comments: "No data on EtKeto acid were provided in the summary to satisfy any of the ecotoxicity endpoints. The test plan indicates that data for BuKeto acid will be used to satisfy the endpoints for EtKeto acid. This is acceptable given the structural similarity of the two chemicals. In addition, ECOSAR values calculated by EPA support the conclusion that BuKeto acid is expected to be more toxic than EtKeto acid."